CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-147

APPROVED DRAFT LABELING

Sinth weights, heoristic survival and development, and incidence of idministrated oral doses of \$40 (but not 270) mg isosorbide monon weight caus and decreased maternal motor activity

Species	Daily Dose	Multiple of MRHD* Based on:		
	(mo/kg)	Body Weight	Body Surface	
Rabbri	810	1013	363	
Rat	900	1125	200	
	540	675	120	
	500	625	118	
,	360	450	80	
	270	338	60	

Calculations assume a human weight of 50 kg and human body surface area of 1.45 m², a rabbd weight of 2 kg and rabbit body surface area of 0.163 m³, and a rat weight of 150 g and rat body surface area of 0.025 m². "Maximum recommended human dose (MRHD) is 20 mg bid.

Rensing Misthers It is not known whether isosorbide monominists is excreted in human milk. Because many drugs are excreted in human milk. Causon should be cercised when isosorbide monominists is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of isosorbide mononitrate in pediatric patients have not been establish

ADVERSE REACTIONS

neverses recent terms.

Headlachs is the most frequent side effect and was the cause of 2% of all dropouts from controlled-clinical trials. He decreased is incidence after the first lew days of therapy.

The following table shows the finguency of adverse reactions observed in 1% or more of subjects in 6 placebo-controlled als, conducted in the United States and abroad. The same table shows the frequency of withdrawal for these adverse reaction in many cases the adverse reactions were of uncertain relation to drug treatment.

Frequency of Adverse Reactions (Discontinuation

Dose Patients	6 Placebo-Controlled Studies					
	Placabo 160	5 mg 54	10 mg 52	-	20 mg 159	
Headache	8%(0%)	17%(0%)	13%(0%)		35%(5%)	
Fatique	2%(0%)	0%(0%)	4%(0%)		1%(0%)	
Upper Respiratory Infection	<1%(0%)	0%(0%)	4%(0%)		1%(0%)	
Pain	<1%(0%)	4%(0%)	0%(0%)		<1%(0%)	
Dizziness	1%(0%)	0%(0%)	0%(0%)		4%(0%)	
Nausea	<1%(0%)	0%(0%)	0%(0%)		3%(2%)	
Increased Cough	<1%(0%)	0%(0%)	2%(0%)		<1%(0%)	
Rash	0%(0%)	2%(2%)	0%(0%)		<1%(0%)	
Abdominal Pain	<1%(0%)	0%(0%)	2%(0%)		0%(0%)	
Allergic Reaction	0%(0%)	0%(0%)	2%(0%)		0%(0%)	
Cardiovascular Disorder	0%(0%)	2%(0%)	0%(0%)		0%(0%)	
Chest Pain	<1%(0%)	0%(0%)	2%(0%)		<1%(0%)	
Diarrosa	0%(0%)	0%(0%)	2%(0%)		0%(0%)	
Flushing	0%(0%)	0%(0%)	2%(0%)		0%(0%)	
Emotional Lability	0%(0%)	2%(0%)	0%(0%)		0%(0%)	
Pruntis	1%(0%)	2%(2%)	0%(0%)		0%(0%)	

Other adverse reactions, each reported by fewer than 1% of exposed patients, and in many cases of uncertain relation to drug treatment, werk:

Cardiovescular: acuse myocardial intarction, apoplexy, arrhythmias, bradycardia, edema, hypertension, hypotension, pallor, palpitations; susurrus aurium, tachycardia.

Sematourinary: Gestrointeetinal, anonasia, dry mouth, dyspepsia, thirst, vomiting, decreased weight.

Gentourinary: prostatic disorder.

Genitourinary: Miscellaneous:

prostatic discrete.
amblyopia, back pain, bitter teste, muscle cramps, neck pain, paresthetia.
arosety, impaired concentration, depression, insomnia, nenousness, inglitmares, restlessness, tramoc verdigo. Neurologic

asthma, dysonea, sinusitis,

Extremely renely, ordinary doses of organic retrains have caused methemoglobinemia in normal-seeming patients; for further discussion of its diagnosis and treatment see under OVERDOSAGE.

OVERDOSAGE descrit Filects

Hemselyszenic Effects
The ill effect of isosorbide mononitrate overdose are generally the results of isosorbide mononitrate's capacity to induce viscodilazation, venous pooling, reduced cardiac output, and hypotansion. These hemselymenic changes may have protest manifestations, including increased infrazonary pressure, with any or all of persistent introblemy headable, contribution, and modernate lever, vertion; pationations: visual dissurbances; nausea and venning (possibly with colic and even bloody diarrhess); syncroge (especially) in the unpritt postural; is in lunger and dyspinas, later (Elicinet by relicted ventilatory efforts) applications; with the stain either flushed or cold and claiminy; heart block and bradycardia; paralysis; coma; secures and death.

Laboratory determinations of serum levels of isosorbide monontryte and its metebolices are not widely available, and such determinations have, in any evers, no established role in the management of isosorbide monontrats overdose.

There are no data suggesting what dose of isosorbide monontraps is likely to be life-threatening in humans. In rate and mice, there is significant initiality at onal doses of 1965 mg/kg and 2581 flig/kg, respectively.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the unne) that might accelerate elimination of isosorbide mononitrate. Isosorbide mononitrate is significantly removed from the blood during fermodialysis.

earnisation of accordance informations: I solicitude information as a generality information from the controlled incomment of the patient's legs may be sufficient, but intravenous infusion of normal sating or similar fluid may also be necessary.

The use of epinephrine or other arterial vesoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expension is not without hazard. Treatment of isosorbide monomitrate overdose in these patients may be subtle and difficult, and invesive monitoring may be

Methemoptoblemmia has been recorded in patients receiving other organic nitrates, and it probably could also occur as a side effect of isosorbide monontrate. Certainly intrate ions liberated during metabolism of isosorbide monontrate can cooks hemoptoble into methemoptoble. Even in patients locally without cyticomine by moticates actively, however, and resuming that instruments of isosorbide monontrate is quantitatively applied to conduction of hemoptoble, about 2 mg/kg of isosorbide monontrates should be required before any of these patients manifests clinically significant (a 10%) methemoptoblemmia. In patients with normal inductions bunction, significant production of methemoptoble should require were larger closes of isosorbide monontrates. In one study in which 36 patients received 2-4 weeks of communication or graph of the study of

Nonwthistanding these observations, there are case reports of significant methemoglobinemia in association with moderate overcoses of organic nitrales. None of the affected patients had been thought to be unusually susceptible.

Mathemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impained corpor delivery despite adequate cardiac output and adequate arenial pO₂. Classically, wethernoglobins-mic blood is described as chocolate brown, without color change on exposure to bir.

When methemographnemia is diagnosed, the trastment of choice is methylene blue, 1 to 2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION
The recommended regimen of isosorbide monoristrate tablets is 20 mg twice daily, with the doses seven hours apart. A starting dose of 5 mg might be appropriate for persons of particularly small stature but should be increased to at least 10 mg by the second or third day of thrapy. Dosage adjustments are not necessary for elderly patients or patients with altered hepatic or

As noted above (CLINICAL PMARMACOLOGY), multiple studies of organic nitrates have shown that maintenance of continuous 24-hour plasma levels results in retractory tolerance. The asymmetric (2 doses, 7 hours apart) disting regimen for isosorbide monornitate subsets provides a disky intrast-iner instance to minimage the development of tolerance.

As also noted under CLINICAL PHARMACOLOGY, well-controlled studies have shown that tolerations to screen monorarate tablets occurs to some extent when using the two-cally regimen in which the two doses are given seven hours spart. This regimen has been shown to have entanginal efficacy beginning one hour after the first close and latting at least seven hours after the state dose and latting at least seven hours after the state dose, the duration (if any) of antangenia activity beyond fourtaen hours has not been studied.

In clinical trials, isosorbide monontrials has been administrated in a variety of regimens and doses. Doses above 20 mg hvice a day (with the doses seven hours spart) have not been adequately studied. Doses of 5 mg levols a day are clearly effectiveness beard on earlies beardone) for only the first day of a hydro---low) (with doses 7 hours spart) regimen.

HOW SUPPLIED

Insporting Monontrate 20 mg Tablets are yellow, round, biconvex, film coated, scored on one side and debosted on the other side with the numbers 1931 and 1761. They are available in bottles of 30, 100 and 1000.

Store at controlled room temperature 15"-30"C (59"-86"F)

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IDE COST 4071-41
ISOSORBIDE MONONITRATE
Tablets
20 mg

N PALETS



ine vid 49741 ISOSORBIDE MONONITRATE Tablets 20 mg



KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP 155, 8497 Manufacturud By: Teva Pharmaceutical Ind. Ltd. Merusalem, 91010, (srae) Aanufacturent For

ISOSORBIDE MONONITRATE Tablets 20 mg Fach tablet contains: Isosorbide Mononitrate

Coutlen: Federal lew prohibits dispensing without prescription.



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1000 TABLETS

NDC 0093-0076-10

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ISOSORBIDE MONONITRATE TABLETS

27

DESCRIPTION

isosorbide monomitate, an organic netrate, is a vasodizator with effects on both arrangs and veins. The chemical name for isosorbide monomitrate is 1,4:3,6-Dianhydro-D-gluottol 5-netrate and the compound has the following structural formula:



CfHNO Isosorbide mononitrata tablets, for onal administration, contain 20 mg of isosorbide mononitrata. In addition, each tablet contains the following inactive ingredients: hydroxypropy callulose, hydroxypropyi methylosikulose, lactose monohydrata, magnesium stearas, microcrystalline callulose, polyethylene glycol, polyethylene

CLINICAL PHARMACOLOGY

Incomplied monometrizes is the major active metabodite of isosorbide diminists (ISDM), and most of the clinical activity of the diminists is attributable to the monomizate.

The arincipal pharmacological action of isospetide mononitrate is relaxation of vascular smooth muscle and consequent dilette-Ine primitipes prasmacological action of describeds monomitists is relaxation of visitation model miscale and consequent distation on of peripheral arteries and visins, especially the latter. Olizion of the vients promotes peripheral pooling of blood and dichasses venous return to the heart, thereby reducing left ventrolar end-disposic presture and pulmonary capitally wedge pressure (praisod). Arteriotar relaxation induces systemic visitations, systolic arterial pressure, and mean arterial pressure (sittational). Oliziation of the connectival arterials are occurs. The relative importance of pressure induction, afterioad reduction and coronary distraction remains undefined.

Pharmscodysamilia:
Dosing regimes for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic intrases. Several well-controded clinical tri-lats have used excress testing to states the amountainful effect of continuously-delivered intrases. In the task pointy of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after intrates have been absent from the body for several hours has their aritanguist efficacy been restored.

The drugh-free interval sufficient to evoid toterance to isoscorbide monomitrate has not been completely defined. In the only regimen of twice-daily according monomitrate has not been completely defined. In the only regimen of twice-daily according monomitrate trained to the next day and the first dose of the next day. Taking account of the next day. Taking account of the restatively long half-life of isosorbide monomitrate trained the country of the next day. Taking account of the restatively long half-life of isosorbide monomitrate this result is consistent with those obtained for other organic nitrates.

The asymmetric twice-daily regimen of isosorbide mononitrate tablets successfully avoided significant rebound/withdrawal effects. The incidence and magnitude of such phenomena have appeared, in studies of other notaties, to be highly dependent upon the schedule of notate soministration.

Pharmarahi salica

Plasmacobiaedical is rapidly and completely absorbed from the gastrointestinal tract. In humans, isosorbide mononitritia is not subject to first pass metabolism in the liver. The absolute bloavailability of isosorbide mononitritia from isosorbide mononitritia in ortical tablets is nearby 100%. Peak plasma concentrations usually occur in bloavd 30-60 minutes. Isosorbide mononitrate authoritia total proportionality over the recommended dose range. Food dose not significantly affect the absorption or bioevalability of isosorbide mononitrate. Memorphism of continuition and the proportional continuities and only of the proportional continuities are not only of the proportional continuities. The volume of distribution is approximately 0.8 L/kg. Plasma protein binding of isosorbide mononitrate was found to be less than 5%.

When radiotabeled isosories monontrate was administered to humans in order to excisite the metabolic false, about held of the dose was found dendrated and renally eccentral as isosories and sorticol. One quarter of the dose was accounted for as conjugates of the parent drug in the unine. None of these metabolities is vascactive. Only 2% of the dose was excisted as

The overall elimination half-life of isosorbide mononicrate is about 5 hours. The rate of clearance is the same in healthy young Another, in papers with various dispress of mast, hepatic, or cardiac dystanction and is the siderly. When radioballed isosoftide monomittes was administered to humans, 33% of the dose was excreted within 46 hours into the urine. Renal excretion was writtenly complete after 5 days; fecal excretion amounted to only 1% of the dose.

Isosorbide mononitrate has no known effect on renal and hepatic function. In patients with varying degrees of renal failure, dosage adjustment does not appear necessary. In patients with liver crimform, the pharmacolainetic parameters after a single dose of isosorbide mononitrate were similar. The values found in healthy volunteers.

Isosorbide monontrata is significantly removed from the blood during hemodialysis; however, an additional dose to compensate for drug local is not necessary. In patients undergoing continuous amountably personnel dialysis, blood levels are similar to patients not on dialysis.

Clastest Wiste
The souts and chronic antianginal efficacy of isosorbide mononstrate has been confirmed in clinical trists. The clinical efficacy of isosorbide mononstrate was studied in 21 stable angina pector's patients. After single dose administration of isosorbide mononstrate, 20 mg, the surrices capacity was increased by 42.7% after one hour, 29.6% after 6 hours, and by 25% after eight hours when compared to placebo. Controlled trists of single doses of isosorbide mononstrate tables have demonstrated that antianginal activity is present about 1 hour after dosing, with peak effect seen from 1-4 hours after dosing.

In one multicenter placeso-controlled trial, isosorbide monontrials was found to be size and shrould using acute and chronic (3 weeks) treatment of angine pectoris. Two hundred fourteen (214) patients were enrosed in the trial; 54 patients were rendembed to receive placeso and 105 patients were into course part. The largest effect of isosorbide monontrials compand to placebo, was on day one - doze one, through 14 hours spart. The largest effect of isosorbide monontrials compand to placebo, was on day one - doze one, through 14 hours shar the first dose of day 14, the increases was about hat of that seen 2 hours after the first doze of day one. On day 21, two hours after the first doze the effect of isosorbide monontrials was 60 to 70% of that seen on day one.

DIDICATIONS AND USAGE

Isosorbide monostrata tablets are indicated for the prevention and treatment of angine pectoris due to coronary artary disease. The orast of action of oral isosorbide mononizrate is not sufficiently rapid for this product to be useful in aborting an acute angunal episode.

CONTRADIONATIONS

ons to organic nitrates are extremely rare, but they do occur. Isosorbide mononitrate is contraindicated in perients

WARKENCS
The benefits of isosorbide monontrate in patients with acute myocardial influction or congestive heart failure have not been established. Because the effects of isosorbide mononstrate are difficult to terminate rapidly, this drug is not recommended in these settings.

If isosorbide monominate is used in these conditions, careful clinical or hemodynemic monitoring must be used to avoid the hist-ards of hypotension and tachycardia.

PRECALITIONS
General
Severe hypotension, particularly with upingfit posture, may occur with even small doses of isosorbide monontrate. This drug should therefore be used with custom in patients who may be volume depleted or who, for whatever reston, are already hypotensions, hypotension induced by isosorbide monontrate may be accompanied by paradioscal briedycardia and increased angina pectoria.

Nitrata therapy may aggrevate the angine caused by hypertrophic cardiomyopathy.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic notrates, tolerance clear-ly occurs. Chest pain, exits myocardia intraction, and even sudden death have occurred during temporary withdrawes of normals from these workers, demonstrating the existence of true physical dependence. The importance of these deservations to the rou-one, clinical use of oral isosorbide monoritate is not known.

Information for Patients
Patients should be told that the amininginal efficacy of isosorbide mononitrate tablets can be maintained by carefully following the prescribed schedule of dosing (two doses taken seven hours apart). For most patients, this can be accomplished by taking

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The asymmetric twice-daily regimen of isosorbide monontrate tabled successfully avoided significant rebound/withdrawal infects. The incidence and magnitude of such phenomena have appeared, in studies of other retrates, to be highly dependent upon the schedule of nitrate administration.

Pharmacokinence

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When radioisbelled accorbide monontrate was administered to humans in order to elucidate the metabolic fals, about hard of the dots was found dentrated and renaity excrused as 6050/0006 and sorteot. One quarter of the dose was accounted for as compagated of the perent drug in the urine. None of these metabolities is viscoactive. Only 2% of the dose was accorded as unchanged drug.

The overall elimination half-life of isosorbide monordrate is about 5 hours. The rate of clearance is the same in hearthy young sourts, in opports with various degrees of innul, hepaits of cardiac dystunction and in the elderly. When radioisbelled isosorbide monornates was administered to humans, 33% of the does was administered within 48 hours into the unine. Renal excretion was virtually complete after 5 days; fecal excretion amounted to only 1% of the does.

including the contract to the contract of the

Isosorbide monontrate is significantly removed from the blood during hemodishysis; however, an additional dose to compensate for drug lost is not necessary. In patients undergoing continuous ambulatory peritoneal dialysis, blood levels are similar to patients not on dialysis.

Classes That and off certification of the property of the control of the control

In one multicenter placebo-controlled trial, isosorbide monoritrate was found to be safe and effective during souts and chronic (3 weeks) treatment of angina pectoris. Two hundred fourtiere (214) paperts were enrolled in the trial; 54 paperts were randomized to receive 10 or 20 mg of isosorbide monoritrate here day seven hours spart. The largest effect of isosorbide monoritrate, compared to placebo, was on day on a does one, and thought of hours start. The largest effect of isosorbide monoritrate, compared to placebo, was on day on a does one, and thought of hours start for first does of day 14, the increase in exercise tolerance due to isosorbide monoritrate was statistically agenticant, the increase was about hat of other seen 2 hours after the first does of day one. On day 21, two hours after the first does the effect of isosorbide monoritrate was 60 to 70% of that seen on day one.

INDICATIONS AND USAGE Isosorbide monomitrate tablets are indicated for the prevention and treatment of angina pector's due to coronary arrany disease. The order of action of oral isosorbide monomitrate is not sufficiently rapid for this product to be useful in aborting an acute anginal epitiode.

CONTRAINDICATIONS

Allergic reactions to organic netrates are extremely rare, but they do occur. Isosorbide mononstrate is contraindicated in patients who are allergic to it.

WARNINGS

The benefits of isosorbide monontrate in patients with acute myocardial interction or congestive heart failure have restablished. Because the effects of isosorbide monontrate are difficult to terminate rapidly, this drup is not recomm

If isosorbide monomitrate is used in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the haz-ards of hypotension and biohycardia,

PRECAUTIONS

us were Severs hypotension, particularly with upright posture, may occur with even small doses of isosorbide monontrate. This drug should therefore be used with causen in patients who may be volume depleted or who, for whatever reason, are aready hypoten-sive. Hypotension induced by isotorbide monontrate may be accompanied by partidoxical bradycardia and increased angine pectoria.

Nitrata therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clear-ly occurrs. Chest pain, acrus myocardial infarction, and even sudden death have occurred during temporary writhdrawel of initrates from these workers, demonstrating the toostmace of true physical dependence. The importance of these observations to the rou-tine, clinical use of oral isosorbide mononitrate is not known.

information for Padests
Patients should be told that the antianginal efficacy of isosorbide mononitrate tablets can be maintained by carefully following the practicular schedule of desiring (two doess taken seven hours apart). For most patients, this can be accomplished by taking the first dose on awakening and the second dose 7 hours late.

As with other nortices, daily headaches sometimes accompany treatment with isosorbide mononitrate. In patients who get these headaches, the headaches are a marker of the activity of the drug. Patients stroud resist the temptation to evoid headaches by altering the schedule of their treatment with isosorbide mononitrate, since loss of headaches may be associated with simultaneous loss of antiargimel efficiary. Aspirin antition exclaminations, on the other hand, other successfully relieve isosorbide mononitrate induced headaches with no deletamous effect on isosorbide mononitrate's antianginal efficacy.

Treatment with isosorbide mononstrate may be associated with light-headedness on standing, especially just after rising from a recumbent or seared position. This affect may be more trequent in patients who have also consumed alcohol.

Orug lateractions
The vascollating effects of isosorbide mononitrate may be additive with those of other vascollations. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Does adjustments of either class of agents may be necessary.

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Cardinageosettis, Matagemental, Impalment of Pertillity

No twidestics of cardinogeneous, Impalment of Pertillity

No twidestics of cardinogeneous, Impalment of insta exposed to isosorbide monomitate in their diets at doses of up to 900 mg/r

tgictary for the first bit months and 500 mg/bg/day for the remaining duration of a study in which makes were dosed for up to 137 weeks. No evidence of matageoristy was seen in whom on the Samonista lest (Ames tast), in numan peripheral lymphocytes, in Chinesa hamister cate (VT9) or, in who in the rat microruscus statl. In a study on the finishing statle presending capacity of two generateors of rists, isosorbide monomitate had no adverse effects on territy or general reproductive performance with oral doses up to 120 mg/kg/day. A dose of 360 mg/kg/day was associated with increased increasing comparisons.)

Prepasacy: Terampenic Effects: Pregnancy Category 8. Reproduction studies performed in rats and rabbits at doses of up to 540 and 510 mg/tg/day, respectively, have revealed no evidency of harm to the fatus due to isosociale monomitate. There are, however, no adequate and velo-controlled studies in originarity women. Because arimal reproduction studies are not always pre-dictive of human response, isosorbide monomitate should be used during pregnancy only of clearly needed.

| Semiablogic | Submation | Su protoco discrete.

Annivoro, lock pain, inter este, muscle cramos, neck pain, peresthesia.

Annivoro, lock pain, international dispression, risonnal, nenousness, nightmeres, restessiness, tremok verdgo.

Estima, dyspene, emiliade.

Extremely rarrely, ordinary doses of organic retrains have caused methemoglobinemia in normal-seeming patients; for further discussion of its diagnosis and treatment see under OVERDOSAGE.

OVERDOSAGE

OVERDIDIDATE

The of effects of isosorbide mononitrate overdose are generally the results of isosorbide mononitrate's capacity to include viscolateation, venues pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have pressure, with any or all of persistent structural pressured intracrusal pressure, with any or all of persistent structural pressured, manufactured in the property of the property with coincident even bloody distributions; causes and vomiting (postably with coincident even bloody distributions; causes and vomiting (postably with coincident even bloody distributions; with income and operations, as the country of the property of the prope

Laboratory determinations of sarum levels of isosorbide mononityse and its metgholites are not widely available, and such determinations have, in any event, no established role in the management of isosorbide mononitrate overdose.

There are no data suggesting what dose or inosorbide monovates in Easily to be life-threatening in humans. In rists and mice, there is significant lethality at onal doses of 1965 mg/kg and 2581 mg/kg, respectively.

No date are evaluable to suggest physiological maneuvers (e.g., maneuvers to change the pH of the unne) that might accelerate elimination of tocoorbide monoritrate. Tocoorbide mononitrate is significantly removed from the blood during hemodialysis.

No specific antiagonist to the viscodiator effects of assorbide mononarize is known, and no intervence has been subject to controlled study as a therapy of isosorbide mononarize overdose. Because the hypotension associated with isosorbide mononarizes overdose is the result of venodiatation and stanial hypovolumia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passave elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epimenhane or other arternal vesoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of isosorbide monomorate overdose in these patients may be suittle and difficult, and investive monitoring may be

Methamoglobinemia has been reported in patients receiving other organic nitrative, and it probably could also occur as a side effect of isosorbide monomitate. Certainly nitrate long liberated during metabolism of isosorbide monomitate can oxidize hemoglobin min methamoglobin. Even in patients totally without organization of hemoglobin, about 2 mg/kg of isosorbide monomitate is quantitatively applied to oxidization of hemoglobin, about 2 mg/kg of isosorbide monomitate should be required before any of these patients manifests calcidity significant (210%) in entire monomitates, and in organization of methomoglobin should be required design any of these patients manifests calcidity significant (210%) in entire discussions of exemptions with ormali reductive function, significant production of methomoglobin should require even larger dose of assorbide monomitates. In one study in which 36 patients increased 2-4 weeks of continuous nerophysinin theritory at 3.1 to 4.4 mg/hr (equivalent, in total administrate dose of instant ions), to 7.6 to 11.1 mg of isosorbide monomitate per hour, the average methomoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected extents had been thought to be unusually succeptible.

Methemoglobin levels are aviable from most clinical faboratories. The diagnosis should be suspected in patients who schib-it signs of imparted corpies delivery despite adequate cardiac output and adequate arterial pO_p. Classically, methemoglobine-mic blood is described as chocolate brown, without color change on exposure to air.

When methemographinemia is diagnosed, the treatment of choice is methylone blue, 1 to 2 mg/kg intravenously.

DOZAGE AND ADMINISTRATION

processes auto accuments trachium.
The recommended regimen of isosorbide monomitrate tablets is 20 mg twice daily, with the doses seven hours apart. A stanting dose of 5 mg might be appropriate for persons of particularly small stature but should be increased to at least 10 mg by the second or third day of therapy. Dosage adjustments are not necessary for adjustly patients or patients with alternal hepatic or renal function.

As noted above (CLIRICAL PHARMACOLOGY), multiple studies of organic nisrates have shown that maintenance of cont 24-hour plasma levels results in nitractory tolerance. The saymmente (2 doses, 7 hours apart) dosing regimen for isos mononitrate tablets provides a daily nitrate-free intervel to minimize the development of tolerance.

As also noted under CLBIECAL PRABILACOLOGY, well-controded studies have shown that obstance to isosorbide monoritrate tablets occurs to some cotent when using the twice-dualy regimen in which the two doese are given series hours apart. This regimen has been shown to have unbanging efficacy beginning one hour airs the first does and lasting at least seven hours after the second does. The duration (if any) of antianginal schirify beyond fourteen hours has not been studied.

In clinical trials, isosorbide monontrate has been administrated in a venety of regimens and doses. Doses above 20 mg twic a day (with the doses seven hours spart) have not been adequately studied. Doses of 5 mg twice a day are clearly effects (affectiveness based on exercise (blerance) for only the first day of a twice-e-day (with doses 7 hours apart) regimen.

HOW SUPPLIED

Invariant Mononimasi 20 mg Tablets are yellow, round, biconvex, film costed, scored on one side and debossed on the other side with the numbers "90" and "76". They are available in bottles of 30, 100 and 1000.

Store at controlled room tamperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured By: TEVA PHARMACEUTICAL BID. LTD. Jerusalem, 91010, Israel

Manufactured For: TEVA PHARMACEUTICALS USA Sellerzville, PA 18960

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